PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/014573	20.12.2004	20.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/00, A61K48/00, A61P35/00, A61P27/00, A61P29/00, A61P43/00

Applicant
BIOINVENT INTERNATIONAL AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/014573

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2 and 5-21

because:

☒ the said international application, or the said claims Nos. 2 and 5-21 with respect to IA relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-21 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1
	No:	Claims	2-21 see separate sheet

2. Citations and explanations

   see separate sheet

1. Concerning section IV

Eight inventions can be distinguished in the present application:

Invention 1: claims 1, 2, 3 (partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is cancer or a solid tumor; a method of eliciting an immune response in a human (eventually at risk or suffering from cancer or from a solid tumor) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being cancer or a solid tumor.

Invention 2: claims 1, 2, 3 (all partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is hemangioma; and a method of eliciting an immune response in a human (eventually at risk or suffering from hemangioma) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being hemangioma.

Invention 3: claims 1, 2, 3 (all partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is ocular neovascularization, diabetic retinopathy or macular degeneration; and a method of eliciting an immune response in a human

(eventually at risk or suffering from the ocular disorders just mentioned) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being ocular neovascularization, diabetic retinopathy or macular degeneration.

Invention 4: claims 1, 2, 3 (all partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is rheumatoid arthritis; and a method of eliciting an immune response in a human (eventually at risk or suffering from arthritis) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being rheumatoid arthritis.

Invention 5: claims 1, 2, 3 (all partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is an inflammatory condition selected from psoriasis, chronic inflammation of the intestines and asthma; and a method of eliciting an immune response in a human (eventually at risk or suffering from said inflammatory disorders) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being an inflammatory condition selected from psoriasis, chronic inflammation of the intestines and asthma. Attention is drawn to the fact that, given the fact that the

three inflammatory diseases mentioned above have a very different pathophysiology, this invention comprises three sub-inventions.

Invention 6: claims 1, 2, 3 (all partially), 5-21 (all partially)

Concern the use of an angiomotin molecule or fragments thereof or of a polynucleotide encoding an angiomotin molecule in the manufacture of a vaccine for vaccinating a subject at a risk of an angiogenesis-related disorder, wherein said disorder is endometriosis; and a method of eliciting an immune response in a human (eventually at risk or suffering from endometriosis) by administering a vaccine comprising an angiomotin molecule or a polynucleotide encoding an angiomotin; a method of generating an immune response against angiomotin in a mammal comprising stimulating ex-vivo immune cells collected from the mammal and transferring the stimulated cells back into the mammal in order to, therapeutically or prophylactically, inhibit the onset or progress of an angiogenesis-related disorder, particularly, the onset or progress of a malignant disease, said disease being endometriosis.

Invention 7: claim 4

Concerns a vaccine effective against blood vessel formation comprising an effective amount of an angiomotin or a polynucleotide encoding an angiomotin.

The problem to be solved by the present application is the provision of prophylactic or therapeutic treatments for hindering blood vessel formation. The solution proposed is the use of an angiomotin molecule, particularly full length human angiomotin or fragments thereof. The use of these molecules allegedly precludes blood vessel formation in general and in a variety of disorders of different pathophysiology, ranging from cancer to asthma and endometriosis in particular. The treatment of each of these different disorders and the general inhibition of blood vessel formation actually represent a solution to a different problem and each is thus considered a separate invention, as indicated above. The only common feature between the different inventions is the reference to an angiomotin molecule or fragments thereof. Since the primary structure of several of these molecules was known before the relevant filing date of the present application (e.g. see WO9966038 and Bratt et al.), reference to them cannot be regarded as a special technical feature within the meaning of Rule 13 PCT. Consequently, the requirement of unity of invention is not fulfilled.

Since searching the different inventions described above would require significant additional search effort, the present search has been limited to the inventions that could be searched with a reasonable search effort (inventions 1 and 7). Therefore, the observation under sections III and V concern only these two searched inventions.

2. Concerning section III

Claims 2 and 5-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3. Concerning section V

3.1 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present **claims 2 and 5-21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3.2 Novelty (Art. 33(2)PCT) and inventive step (Art. 33(3) PCT)

3.2.1 WO03037931 (see pg. 5, lines 14-20; pg. 7, lines 5-12; pg. 86, line 1-5; pg. 119, lines 20-25; pg. 138, lines 25-35) discloses angiomotin molecules similar to human angiomotin and suggests that these molecules play a role similar to the latter in angiogenesis. This document also

refers to the therapeutic potential of said molecules in cancer treatment (pg. 138, lines 25-35) and concretely to their use as vaccines to elicit a humoral and/or cellular immune response (pg. 48, lines 5-9; pg. pg. 81, lines 15-20; pg. pg. 92, line 33; pg. 127, lines 17 and 18). Hence, novelty cannot be acknowledged for **claim 4** - a product claim directed to a vaccine comprising *an angiomotin molecule* or a polypeptide encoding and angiomotin molecule.

3.2.2 With regard to invention 1, the following comments are pertinent:

a) In view of the comments under item 3.2.1, it is clear that WO03037931 discloses the use of an angiomotin molecule as a vaccine to treat/prevent angiogenesis-related disorders. Hence, **claims 1-3, 5 and 6** appear to lack novelty. In the unlikely event that formal novelty over this document could somehow be established, inventive step would still have to be substantiated.

b) The prior art describes the use of human angiomotin and of antibodies against it for the treatment of angiogenesis-related disorders (WO9966038; pg. 9, lines 25-29 and claim 29); provides evidence that human angiomotin is a cell surface-associated protein expressed in capillary endothelial cells and that it stimulates angiogenesis by increasing cell motility (see Troyanovsky et al. and Levechenko et al.); shows that angiomotin is highly expressed in human breast tumors, its expression being correlated with tumor metastatic activity probably through the induction of angiogenesis (Jiang et al.).

Taking Jiang et al. as the closest prior art, the technical problem is the provision of a vaccine for vaccinating subjects with or at risk of an angiogenesis-related disorder, especially cancer or a solid tumor. The person skilled in the art, when faced with this problem would be aware of the prior art described above and of the fact that: i) the closest prior art states clearly suggests that "angiomotin may be a possible target in cancer and angiogenesis therapies"; ii) vaccine strategies targeting the vasculature are known to have the advantage of (theoretically) avoiding resistance and of preventing the growth of different cancer types, since angiogenesis plays a role is most of these disorders) (see Scappaticci et al.). The person skilled in the art would thus conclude that angiomotin would be a suitable solution for a vaccine against angiogenesis-related disorders, especially cancer or solid tumors, thus arriving at the solution proposed by the application. Therefore, claims 1-21 do not appear to involve inventive step.

It should be particularly be borne in mind that the present application does not show that

fragments of human angiomotin can solve the technical problem. Similarly, evidence, other than that derivable from the prior art (by combining Jiang et al. with Brossart et al), that the method of claims 16-21 would solve the technical problem is also not provided.